

WHAT IS CLAIMED IS:

1. A nucleic acid construct comprising: at least one stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO:1; and a heterologous nucleic acid sequence operatively linked to the regulatory sequence, wherein expression of the heterologous sequence is regulated by the non-coding sequence and wherein the heterologous sequence encodes a therapeutic agent effective for treating a cell proliferative disorder.
2. The nucleic acid construct of claim 1, wherein the non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) is derived from the glucose responsive protein 78 (grp78) promoter sequence.
3. The nucleic acid construct of claim 2, wherein the glucose responsive protein 78 (grp78) promoter sequence comprises a sequence from about 3000 base pairs 5' of the site of initiation of transcription of the grp78 coding sequence to 200 base pairs 3' of the site of initiation of the grp78 coding sequence.

4. The nucleic acid construct of claim 1, wherein the non-coding regulatory sequence comprises a transcriptional and translational initiation region.

5 5. The nucleic acid construct of claim 4, further comprising a transcriptional termination region functional in an animal cell.

6. The nucleic acid construct of claim 1, wherein the therapeutic agent is a biologically active protein.

10 7. The nucleic acid construct of claim 6, wherein the biologically active protein is an enzyme that converts a non-therapeutically effective compound to a therapeutically effective compound.
Prodrug *drug*

15 8. The nucleic acid construct of claim 7, wherein the enzyme is selected from the group consisting of HSV thymidine kinase, VSV thymidine kinase, deoxycytidine kinase, cytosine deaminase or nucleoside phosphorylase.

20 9. The nucleic acid construct of claim 7, wherein the non-therapeutically effective compound is selected from the group consisting of ganciclovir, acyclovir, 6-methoxypurine

arabinoside (Ara-M), cytosine arabinoside or cytarabine (Ara-C), fludarabine, 2-chlorodeoxyadenosine, difluorodeoxycytidine, 5-fluorocytidine and 6-methylpurine-2'-deoxyriboside (MeP-dr).

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10. The nucleic acid construct of claim 1, wherein the therapeutic agent is antisense RNA for disrupting expression of an endogenous coding sequence.

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11. The nucleic acid construct of claim 10, wherein the endogenous coding sequence is an oncogene.

12. The nucleic acid construct of claim 11, wherein the oncogene is selected from the group consisting of ABL, ERBB-1, ERBB-2 (NEU), GIP, GSP, MYC, L-MYC, N-MYC, H-RAS, RET, ROS, K-SAM, SIS, SRC, C-FOS, C-JUN, PRAD1 AND TRK.

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13. The nucleic acid construct of claim 1, wherein the therapeutic agent is a tumor suppressor protein, or biologically active fragment thereof.

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14. The nucleic acid construct of claim 13, wherein the tumor suppressor protein, or biologically active fragment

thereof, is selected from the group consisting of p53, RB, WT1 (Wilms Tumor) and NF1 (neurofibromatosis).

15. The nucleic acid construct of claim 1, wherein the cell proliferative disorder is a neoplastic disorder.

16. The nucleic acid construct of claim 1, wherein the cell proliferative disorder is associated with inflammation.

17. A nucleic acid construct comprising: at least one stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO:1; and a heterologous nucleic acid sequence operatively linked to the regulatory sequence, wherein expression of the heterologous sequence is regulated by the non-coding sequence and wherein the heterologous sequence encodes a detectable marker.

18. The nucleic acid construct of claim 17, wherein the detectable marker is a visually detectable marker.

19. The nucleic acid construct of claim 18, wherein the visually detectable marker is green fluorescent protein (GFP), or biologically active derivative thereof.

20. The nucleic acid construct of claim 17, wherein the detectable marker is a biologically active protein.

21. The nucleic acid construct of claim 20, wherein the biologically active protein is an enzyme.

22. A nucleic acid construct comprising: at least one stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO:1; and a heterologous nucleic acid sequence operatively linked to the regulatory sequence, wherein expression of the heterologous sequence is regulated by the non-coding sequence and wherein the heterologous sequence encodes a therapeutic agent effective for treating a disorder associated with glucose starvation.

23. The nucleic acid construct of claim 22, wherein the detectable marker is a biologically active protein.

24. The nucleic acid construct of claim 23, wherein the biologically active protein is an enzyme.

25. The nucleic acid construct of claim 22, wherein the therapeutic agent is antisense RNA for disrupting expression of an endogenous coding sequence.

5 26. A recombinant vector comprising the nucleic acid construct of claim 1, claim 17 or claim 22.

27. The recombinant vector of claim 26, wherein the vector is an animal cell expression vector.

10 28. The recombinant vector of claim 26, wherein the vector is a viral vector.

15 29. The recombinant vector of claim 28, wherein the viral vector is selected from the group consisting of retroviral vectors and DNA viral vectors.

30. The recombinant vector of claim 28, wherein the retroviral vector is designated G1NaGRPTK.

20 31. A pharmaceutical composition comprising the nucleic acid construct of claim 1, claim 17 or claim 22 in a pharmaceutically acceptable carrier.

32. The pharmaceutical composition of claim 31 in a controlled release formulation.

33. The pharmaceutical composition of claim 31 in a liposomal formulation.

34. The pharmaceutical composition of claim 31 in a lyophilized form.

35. The pharmaceutical composition of claim 31 in a unit dose form.

36. A method of providing increased transcription of a nucleic acid sequence in a targeted tissue of an animal comprising introducing into the animal the nucleic acid construct of claim 1, claim 17 or claim 22.

37. A method for inhibiting cell proliferation comprising contacting a target cell capable of cell proliferation with a nucleic acid construct of claim 1, claim 17 or claim 22.

38. A method for treating a cell proliferative disorder in a subject comprising administering to the subject a nucleic acid construct of claim 1 or claim 22.

39. The method of claims 38, wherein the subject is a mammal.

40. The method of claim 39, wherein the mammal is a mouse.

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41. The method of claim 39, wherein the mammal is a human.

42. The method of claims 38, wherein the administration is by
in vivo administration.

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43. The method of claim 42, wherein the in vivo administration
is by systemic, local, or topical administration.

44. The method of claims 38, wherein the administration is by
ex vivo administration.

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45. The method of claims 38, wherein the cell proliferative
disorder is a neoplastic disorder.

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46. The method of claim 45, wherein the neoplastic disorder is
selected from the group consisting of lung cancer, colon-
rectum cancer, breast cancer, prostate cancer, urinary
tract cancer, uterine cancer lymphoma, oral cancer,
pancreatic cancer, leukemia, melanoma, stomach cancer,

thyroid cancer, liver cancer, and brain cancer and ovarian cancer.

5 47. A method for detecting a cell proliferative disorder in a subject comprising administering to the subject a nucleic acid construct of claim 17.

48. A transgenic non-human animal comprising a nucleic acid construct according to claim 1, claim 17 or claim 22.

10 49. A transgenic cell comprising a nucleic acid construct according to claim 1, claim 17 or claim 22.

15 50. A transgenic non-human animal having a phenotype characterized by expression of a heterologous nucleic acid sequence encoding a detectable marker otherwise not naturally occurring in the animal, the phenotype being conferred by a transgene contained in the somatic and germ cells of the animal, the transgene comprising the
20 heterologous nucleic acid sequence operably associated with at least one stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO:1.

51. The transgenic non-human animal of claim 50, wherein the non-coding regulatory sequence is derived from the glucose responsive protein 78 (grp78) promoter sequence.

5 52. The transgenic non-human animal of claim 51, wherein the glucose responsive protein 78 (grp78) promoter sequence comprises a sequence from about 3000 base pairs 5' of the site of initiation of transcription of the grp78 coding sequence to 200 base pairs 3' of the site of initiation of the grp78 coding sequence.

10 53. The transgenic non-human animal of claim 50, wherein the non-coding regulatory sequence comprises a transcriptional and translational initiation region.

15 54. The transgenic non-human animal of claim 50, further comprising a transcriptional termination region functional in an animal cell.

20 55. The transgenic non-human animal of claim 50, wherein the animal is a mammal.

56. The transgenic non-human animal of claim 55, wherein the mammal is a mouse.

57. A transgenic non-human animal having a phenotype characterized by expression of a heterologous nucleic acid sequence encoding a therapeutic agent effective for treating a cell proliferative disorder otherwise not naturally occurring in the animal, the phenotype being conferred by a transgene contained in the somatic and germ cells of the animal, the transgene comprising the heterologous nucleic acid sequence operably associated with at least one stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO:1.

58. A method for producing a transgenic non-human animal having a phenotype characterized by expression of a heterologous nucleic acid sequence encoding a detectable marker otherwise not naturally occurring in the animal, wherein said heterologous nucleic acid sequence is operably associated with at least one stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO:1, the method comprising:

- a) introducing at least one transgene into a embryo of an animal, the transgene comprising at least one stress-

responsive non-coding regulatory sequence comprising
at least two endoplasmic reticulum stress elements
(ERSE) as set forth in SEQ ID NO:1 isolated upstream
from the heterologous nucleic acid sequence encoding a
detectable marker;

- b) transplanting the embryo into a pseudopregnant animal;
- c) allowing the embryo to develop to term; and
- d) identifying at least one transgenic offspring
containing the transgene.

59. The method of claim 58, wherein the introducing of the
transgene into the embryo is by introducing an embryonic
stem cell containing the transgene into the embryo.

60. The method of claim 58, wherein the introducing of the
transgene into the embryo is by infecting the embryo with a
retrovirus containing the transgene.

61. The method of claim 58, wherein the transgenic non-human
animal is a mammal.

62. The method of claim 61, wherein the mammal is a mouse.